iPS cells from women create model for muscular dystrophy, X-linked diseases

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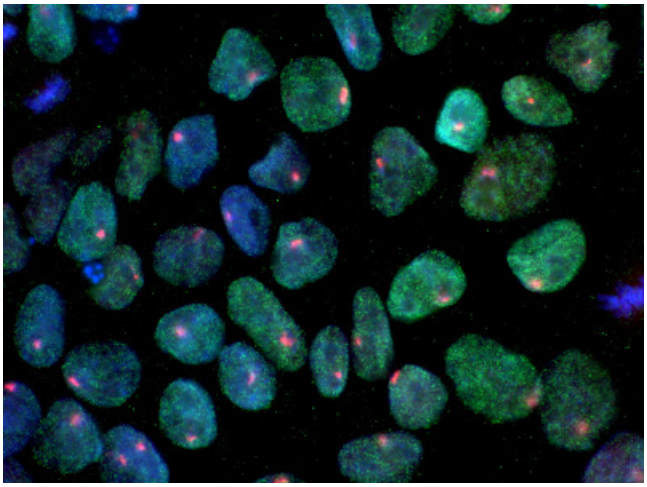

Reprogrammed skin cells showing inactivated X in red

CIRM grantees at the University of California, Los Angeles have uncovered a feature of reprogrammed iPS cells that make them uniquely excellent for understanding diseases that arise from mutations on the X chromosome.

First some background. Men inherit an X chromosome from their mother, which contains many thousands of genes, and a Y from the father, which does little except confer manhood. Women inherit one X chromosome from each parent. Those female cells overcome their genetic overabundance by shutting down, at random, one of the two X chromosomes, putting the cells at genetic par with male cells.

But the two aren't really equal. If men inherit a mutation on an X chromosome, it is present in every cell of the body and can cause muscular dystrophy, Rett Syndrome, color-blindness and other disorders. Women who inherit a mutation on an X chromosome from one parent will only show that mutation in half their cells. The other half of the body's cells, with the non-mutated chromosome active, can generally compensate.

So what does this have to do with reprogrammed cells and disease modeling? It turns out that the process of reprogramming skin cells into embryonic-like induced pluripotent stem cells doesn't overturn the inactivated X. Reprogramming cells from a woman's skin sample will produce two distinct types of iPS cell lines; half with one X active, and half of with the other X active. If one of those two chromosomes carries a mutation, say, for muscular dystrophy, some of those iPS lines will also display that mutation.

In a press release from UCLA, senior author Kathrin Plath said:

> "This non-random pattern of X chromosome inactivation found in iPS cell lines has critical implications for clinical applications and disease modeling and could be exploited for a unique form of gene therapy for X-linked diseases."

In a publication in *Cell Stem Cell*, Plath and her colleagues report that they created iPS cell lines from a woman who had inherited one X chromosome carrying a mutation that can cause muscular dystrophy. The other X chromosome had a normal copy of the gene. Scientists can now mature both groups of cells into skeletal muscle and compare the resulting tissue as a way of understanding-and perhaps one day treating-the devastating disease.

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CIRM funding: Sean Sherman (TG2-01169), Kathrin Plath (RN1-00564), William Lowry (RS1-00259), Jerome Zack. (RL1-00681)

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